(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/000344 A1

(51) International Patent Classification[7]: A61P 41/00, A61K 31/683, 31/685 // (A61K 31/685, 31:683)

(21) International Application Number: PCT/GB02/02915

(22) International Filing Date: 25 June 2002 (25.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0115505.0 25 June 2001 (25.06.2001) GB

(71) Applicant *(for all designated States except US)*: **BRITANNIA PHARMACEUTICALS LIMITED** [GB/GB]; 41/51 Brighton Road, Redhill, Surrey RH1 5TS (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HILLS, Brian, Andrew** [AU/AU]; 44 Bowsprit Parade, Cleveland, QLD 4163 (AU). **WOODCOCK, Derek** [GB/GB]; Britannia Pharmaceuticals Limited, 41/51 Brighton Road, Redhill, Surrey RH1 5TS (GB).

(74) Agent: **BROOKES BATCHELLOR**; 102-108 Clerkenwell Road, London, EC1M 5SA (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/000344 A1

(54) Title: USE OF PHOSPHOLIPIDS FOR THE PREVENTION 0F SURGICAL ADHESIONS

(57) Abstract: A surface active phospholipid (SAPL) composiiton in the form of a solution, dispersed or especially a paste comprising DPPC (dipalmitoyl-phospatidyl-choline) is used to reduce the risk of adhesions after surgery, especially open surgery on the spine, tendons or peripheral nerves.

USE OF PHOSPHOLIPIDS FOR THE PREVENTION OF SURGICAL ADHESIONS

Field of the Invention

This invention relates to the use of surface active phospholipids (SAPL) to reduce the risk of adhesions after surgery.

Background of the Invention

SAPL is used clinically for the treatment of respiratory distress syndrome (RDS) in neonates. In this role, it has been assumed that the SAPL functions by reducing the high surface tension forces at the air-water interface within the alveoli, thereby reducing the pressure needed to expand the lungs, see Bangham et al., Colloids & Surfaces, 10 (1984), 337 to 341.

Post-surgical adhesions are the single greatest complication of many surgeries. Post-surgical adhesions are fibrous attachments between tissues that can form inside the body following surgery. Internal tissues that would normally be separate become joined by fibrous scar tissues called adhesions, as a result of the body's normal healing process. Complications from post-surgical adhesions can include chronic back or pelvic pain, intestinal obstruction and infertility. Complications can be severe enough to require re-operation, but adhesions can make subsequent surgeries more difficult to perform.

Surgical adhesions continue to pose a problem as a major cause of female infertility (Trimbos-Kemper T, Trimbos B, van Hall E. Etiological factors in tubal infertility. *Fertil. Steril.* 1982: **37**: 384-8), while intraperitoneal adhesions are the main cause of intestinal obstruction following surgery (Menzies D, Ellis H. Intestinal obstruction from adhesions: How big is the problem? *Ann. R. Coll. Surg. Engl.* 1990: **72:** 60-3).

Postsurgical adhesions following back surgery are one of the leading causes of recurrent back pain. It is widely recognised that postsurgical adhesions play a major role in poor patient outcome following surgery, or failed back syndrome. Failed back surgery syndrome is seen in 10-40 percent of patients who undergo back surgery.

Postsurgical adhesions are also a significant problem after tendon surgery. Following tendon surgery, adhesions can inhibit the tendons' ability to glide, thereby limiting motion. In peripheral nerve surgery (e.g. carpal tunnel syndrome) adhesions may cause tethering and compression of nerve roots, leading to pain and loss of function.

A number of agents and methods have been employed to minimise adhesion formation with varying degrees of success, including the use of:

corticosteroids (Hockel M, Ott S, Sieman U, Kissel T. Prevention of peritoneal adhesions in the rat with sustained intraperitoneal dexamethasone delivered by a novel therapeutic system. *Ann. Chir. Gynaecol.* 1987: **76**: 306-13),

non-steroidal anti-inflammatory drugs (DeSimone JM, Meguid MM, Kurzer M, Westervelt J. Indomethacin decreases carrageenan-induced peritoneal adhesions. *Surgery* 1988: **104**: 788-95),

calcium channel blockers (Steinleitner A, Lambert H, Montoro L, Kelly E, Swanson J, Sueldo C. The use of calcium channel blockade for prevention of postoperative adhesion formation. *Fertil. Steril.* 1988: **50**: 818-21),

plasminogen activators (Menzies D, Ellis H. Role of plasminogen activator in adhesion prevention. *Surg. Gynaecol. Obstet.* 1991: **172**: 326-66), and

'bioresorbable' mechanical barriers (Goldberg EP, Sheets JW, Habal MB. Peritoneal adhesions. Prevention with the use of hydrophilic polymer coatings. *Arch. Surg.* 1980: **115**: 776-8; Best CI, Rittenhouse D, Vasquez C, Norng T, Subias E, Sueldo CE. Evaluation of Intercede (TC7) for reduction of postoperative adhesions in rabbits. *Fertil. Steril.* 1992: **58**: 817-20; Burns JW, Colts MJ, Burgees LS, Skinner KC. Pre-clinical evaluation of Seprafilm bioresorbable membrane. *Eur. J. Surg.* 1997: **577**: S40-8), which can introduce their own problems.

WO 91/12026 (McNaught Medical) discloses a method of reducing surgical adhesions by means of coating tissue surfaces with a phospholipid, preferably

lecithin, in suspension or solution in an inert carrier, such as for example, water, saline, or propylene glycol, or mixtures thereof.

Also, WO 99/51244 (Britannia) describes the use of powdered phospholipids to prevent surgical adhesions.

US Patent 6133249 (McNaught Medical) describes a method of lubricating mammalian joints using a liquid composition comprising of phospholipids dispersed in propylene glycol.

Summary of the Invention

The present invention is based on the surprising discovery that liquid, semi-liquid or pasty compositions of certain phospholipids dispersed in a physiologically acceptable carrier are equal to or better than the compositions of WO 99/51244 in reducing the risk of surgical adhesions.

The powder compositions of WO 99/51244 have the advantage that they are easily administered into body cavities such as the peritoneum by simple "puffers" or other gas stream delivery devices. The advantage of the liquid, and especially the paste, compositions of this invention is that the surgeon can apply the composition as a directed, substantially non-mobile, "slug" to be spread manually using a gloved finger, or apply compositions manually using a gloved finger directly to the desired site, and immediately check visually that the intended area is covered. This is especially advantageous in open surgery, such as on flexor tendons of the hand, or spinal surgery, or peripheral nerve surgery.

In one aspect the present invention provides a method of reducing the risk of surgical adhesions which comprises applying a composition comprising a SAPL to surfaces adjacent an incision during surgery, characterised in that the SAPL is DPPPC, or a mixture of DPPC and PG, or DPPG, dispersed in a physiologically acceptable non-volatile carrier liquid.

In another aspect the present invention provides the use of a SAPL to prepare a medicament for reducing the risk of adhesions following surgery, characterised in that the SAPL is DPPC or a mixture of DPPC and PG or DPPG, dispersed in a physiologically acceptable non-volatile carrier liquid.

The carrier liquid is one which is substantially non-volatile or only sparingly volatile at body temperature. Suitable carriers include physiologically acceptable glycols, especially propylene glycol, polyethylene glycols and glycerol.

The SAPL may be dispersed in the carrier so as to form liquid, semi-liquid or pasty compositions. Semi-liquid or paste compositions are preferred because they can be applied and spread by a surgeon using a gloved finger, and are particularly suitable for use in open surgery where the surfaces abraded by surgery are well defined and easily accessible.

Brief Description of the Drawing

The Figure shows the sites for administration of SAPL compositions of this invention during tendon surgery.

Detailed Description of the Invention

Pastes can be prepared by simply dispersing a SAPL powder in the carrier, or when appropriate dissolving the SAPL in heated carrier and allowing the SAPL to precipitate as a powder on cooling, preferably at a loading that will form a paste. A thick paste of the SAPL and carrier is ideal to apply to open wounds to which it adheres well. It enables a much higher concentration of the SAPL to be applied to the incision site.

Propylene glycol is especially effective as a carrier because at room temperature SAPL may be dispersed in it as a paste, but at body temperature a mobile solution is formed. A paste of 400 mg/ml of DPPC in propylene glycol has been shown to give 93% protection against adhesions in surgical tests, as described in the experiments below.

If desired, the pasty compositions of this invention may be applied to surgical sites in conjunction with the powder compositions of WO 99/51244 (Britannia), the latter being used to coat and protect more peripheral areas.

Various dispersions of SAPL in propylene glycol are described in US Patent 6133249, the entire contents of which are incorporated herein by reference. Similarly the powder compositions of WO 99/51244 may be dispersed in a carrier such as propylene glycol, and the entire disclosure of WO 99/51244 is also incorporated herein by reference.

In other medical uses of SAPL, spreading agents, especially PG, have been believed to enhance or potentiate the binding of DPPC to an epithelial surface. Surprisingly in the present invention, compositions based on DPPC alone have out-performed compositions based on DPPC/PG which have been especially effective in the situations covered by the patent applications acknowledged above.

A further surprising finding is that pastes prepared by dispersing coarse SAPL particles, for example around 10μm in size, are more effective than when using fine SAPL particles, such as around 5μm in size. More generally, the powdered SAPL may have a particle size in the range of 0.5 to 100μm, more suitably of 0.5 to 20μm, preferably 0.5 to 10μm.

The compositions may also include preservatives where appropriate, such as fungicides, bactericides and anti-oxidants.

The solutions/dispersions/pastes of the present invention are especially suitable for surgical procedures where there is a potential for adhesion in areas that are difficult to access by powder sprays. The Figure of the accompanying drawing shows a situation arising in tendon surgery where both a tendon (1) and its sheath (2) are cut through and require stitching back together. By means of a catheter (3), a solution dispersion or paste composition of the invention may be introduced between the tendon and the sheath to prevent adhesions that impair mobility.

The same situation applies in spinal surgery where the spinal cord is damaged within the spinal cord sheath, and with surgery on other nerves.

The viscosity of the solution/dispersion/paste may be varied to suit specific surgical sites or the preferences of individual surgeons. For example, in difficult to access areas (e.g. flexor tendons) a relatively low viscosity fluid may be used, whereas at a site where gravity will effect its distribution a higher viscosity composition may be preferred. Temperature will play a part in the viscosity of the compositions. Typically a range of 0.1 -10 000 cP may be considered. However, formulations outside this range may be required for specific applications at the discretion of the surgeon.

Further details of the invention are illustrated in the following experiments.

MATERIALS

Animals

Eighty New Zealand white rabbits, weighing between 2 and 3kg were used since this breed has been found to be a good model for surgical adhesions (Bhandarkar DS, Nathanson LK, Hills BA. Spray of phospholipid powder reduces peritoneal adhesions in rabbits. *Aust. N.Z. J. Surg.* 1999: **69**: 388-90). They were given access to food pellets and water *ad libitum* before and after the operation.

Release agent/lubricant

The phospholipid mixture (Pumactant) was supplied by Britannia Pharmaceuticals Ltd, Redhill, U.K. Coarse Pumactant is a dry powder of 10μm particle size of a mixture of 70% DPPC and 30% egg PG co-precipitated from solution and, therefore, intimately mixed. Fine Pumactant has the same composition but has a particle size of 5μm. The DPPC is *Lα* - DPPC, which is the optical isomer which occurs naturally and is digested by phospholipases. *Lα* - DPPC was supplied by Lipoid GmbH, Ludwigshafen, Germany, who also supplied the dipalmitoyl phosphatidylglycerol (DPPG). The solvent used was clinical grade propylene glycol and all solutions were made to a concentration of 400mg/mL of total phospholipid (i.e. DPPC + DPPG) per

mL at 60°C which reverted to pastes at room temperature. The compositions used were DPPC alone, DPPG alone, 7:3 DPPC:DPPG and 1:1 DPPC:DPPG.

METHODS

The protocol for the study was approved by the University of Queensland Animal Experimentation Ethics Committee.

Operation

General anaesthesia was induced by a combination of intravenous ketamine (Parnell Laboratories, NSW) and xylazine (Ilium Xylazil: Troy Laboratories, NSW) and maintained by xylazine alone. Common to all procedures were aseptic operative conditions consisting of iodine for skin preparation, drapes to minimise contamination of the peritoneal cavity and non-powdered gloves worn by both the surgeon and assistant. Each animal underwent a lower midline laparotomy for creation of a standard separate 5 x 1cm parietal peritoneal defect (marked with a silk suture at each end) sited to lie adjacent to a matching 5 x 1cm visceral peritoneal defect over the adjacent caecum. At the conclusion of the procedure the abdomen was closed with continuous 4/0 polybutester (Novafil, David Geck, Quebec) in two layers including the peritoneum.

Experiments

Ten animals did not have any further intervention except as described above and provided the controls (Group I). In 20 animals a 1mm I.D. polyethylene tube was placed intraperitoneally adjacent to the caecal intraperitoneal defect and exteriorised through a subcutaneous tunnel. Ten of these rabbits (Group II) received an intraperitoneal puff of Fine ALEC (100mg) via a purpose-built device prior to abdominal closure. Another 10 animals (Group III) received Coarse Pumactant powder, i.e. the same material as used in a previous study (21).

In 10 animals (Group IV) 1mL of propylene glycol was applied directly to the defect on the surface of the large bowel by means of a hypodermic syringe to which no needle was fitted. This procedure was repeated in a further 40 rabbits in which one of four phospholipid compositions were substituted for the propylene glycol and applied

as paste. In the first 10 of these animals, the paste was $L\alpha$ - DPPC (Group V). In the next 10 rabbits (Group VI) the paste was DPPG; in the next 10 (Group VII) it was 7:3 DPPC:DPPG, while in the last 10 (Group XIII) it was 1:1 DPPC:DPPG.

One week after the operation, the rabbits were killed by an overdose of pentobarbitone (Lethabarb, Virbac, NSW) and a postmortem performed to assess the extent of adhesion formation. An adhesion is defined as any connection between bowel and the healed 5 x 1cm parietal peritoneum marked by the silk sutures. Adhesions formed occasionally on the undersurface of the wound, but were not analysed. Treatment was performed by one surgeon who also performed the postmortems.

Statistics

The various groups were compared using a simple Student's *t*-test since there were equal numbers of subjects in each comparison - see Table 2. A *p*-value of 0.05 or below was regarded as significant.

RESULTS

The results for the eight groups are given in Table 1 and depicted with errors of the mean in Figure 1. The protection rates (PR) quoted in Table 1 are calculated as:

PR = 100 [1 - (adhesion length/adhesion length of controls)]%.....(1)

The following features warrant special mention:

1. The Coarse Pumactant produced a highly significant (p= 0.005) reduction in adhesions to 8.4 ± 3.6 (mean ± sem) compared to controls of 29 ± 5.4, corresponding to a protection rate of 71%

2. The Fine Pumactant was less effective than the Coarse Pumactant, the protection rate of 37% failing to reach 95% significance over controls.

3. Propylene glycol alone offered no protection relative to controls.

4. The pastes all gave significant protection from adhesions apart from pure DPPG, the efficacy increasing as the proportion of DPPG was decreased.

5. The best performance was that of DPPC paste which amounted to a protection rate of 93% relative to controls.

6. This performance was better than that of Coarse Pumactant, although a direct comparison did not reach statistical significance ($p = 0.15$).

DISCUSSION

The particularly encouraging feature of the results for dry powders was the reproducibility of the protection rate of 71% for Coarse Pumactant by comparison with an earlier study (Bhandarkar *et al*, *supra*) performed by a different surgeon using the identical material. A dry powder which can be 'puffed' on to the incision and surrounding area still offers a much simpler mode of application than approaches requiring very careful positioning of a thin digestible film as a gross physical barrier.

The results for Fine Pumactant (5μm) were surprising in so far as a larger surface area of DPPC/PG might have been expected to prove more protective than its Coarse (10μm) competitor. The lower efficacy could be attributed to the use of a co-powder mixture of DPPC and Egg PG as opposed to Coarse Pumactant in which co-precipitation from an organic solvent ensures mixing at the molecular level. Another factor might be wider dispersion of the same dose of powder, leaving less in the test area. Wide dispersion could prove a benefit in cases of abdominal trauma where bile salts escaping from the gut could have stripped the peritoneal cavity of its protective lining of SAPL, just as they can in the stomach (Hills BA (1989). Oligolamellar lubrication of joints by surface-active phospholipid. *J. Rheumatol.* **16**: 82-91).

Where DPPC and PG are used in the same proportion, viz. 7:3, there is not much difference (71% vs 80%) in protection between powder and paste. This could be explained by the difference in dose, which was higher for the paste. However comparable the protection rates, they amount to a ratio of 29 *versus* 20 in the number of residual adhesions, i.e. a 30% difference.

Pursuing the theme of residual adhesions, the ratio extends to 84 for Coarse Pumactant *versus* 21 for DPPC paste, i.e. a ratio of 4:1 - see Table 1. Moreover only 1 animal in 10 displayed any adhesions at all with the paste. This is an important consideration in the clinical setting where any adhesions at all could result in a patient returning to surgery for their resection.

Hence, for cases where the boundaries of surgical intervention are well defined the DPPC paste offers an exciting and possibly more efficient means of preventing surgical adhesions. It is very simple to apply either by a hypodermic syringe without a needle or by simply smearing on the material with a gloved finger or any other mode of application which the individual surgeon may prefer. The DPPC paste is easy to autoclave (20 mins. at 121°C) in its container which can be a vial or hypodermic syringe. It can also be sterilised in its container by γ-irradiation.

One great advantage of the paste is our past experience of using the same product (at half concentration) as a lubricant in the joint for treating osteoarthritis (OA) in 10 humans (Vecchio P, Thomas K, Hills BA. (1999). Surfactant treatment for osteoarthritis. *Rheumatology.* **38**: 1020-1021) and its equine equivalent - degenerative joint disease - in 130 horses. We have had only two adverse reactions - one human and one equine. Both cases were "gouty reactions" attributed to "unidentified crystals" found in the synovial fluid aspirated from the joints. In those investigations the problem was attributed to crystals of DPPC separated from solution in propylene glycol. In subsequent clinical trials the paste was autoclaved within 2 days of injection and this has eliminated the problem. We have subsequently studied the crystallisation of DPPC from its supersaturated solutions (200mg/mL propylene glycol); although crystals may not prove such a problem between surfaces which are not weight-bearing. Incidentally propylene glycol is FDA-approved as a lipid vehicle for i.v. and i.m. administration.

Finally there are many clinical studies of the intraperitoneal injection of SAPL in its various forms *into the peritoneal cavity* with the intention of restoring ultrafiltration in CAPD as reviewed elsewhere (Hills BA, (2000). Role of surfactant in peritoneal dialysis. *Perit. Dial. Internat.* **20**: 503-515). In that review we could find no cases

of inflammatory reaction reported, although all except one animal study used SAPL as an aqueous suspension.

In conclusion it can be stated that, whereas dry Pumactant powder offers a good, safe and reproducible means of preventing about 70% of adhesions, the paste formulation offers a cheaper means of reducing those residual adhesions a further four-fold.

TABLE 1: NUMBER OF ADHESIONS FORMED PER ABRADED AREA (5x1cm) IN RABBITS

Group	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**
TREATMENT	CONTROL	Fine Pumactant powder	Coarse Pumactant powder	Propylene Glycol only	DPPC paste	DPPG paste	DPPC:DPPG 7:3 paste	DPPC:DPPG 1:1 paste
Adhesion Length (mm)	38	0	0	0	0	0	0	0
	36	0	0	0	0	0	0	0
	25	0	23	50	0	0	0	0
	36	50	0	0	21	0	0	0
	46	0	19	0	0	0	0	0
	30	37	0	50	0	0	37	0
	29	0	28	50	0	0	0	0
	50	27	0	50	0	37	0	0
	0	28	14	50	0	43	0	32
	0	40	0	0	0	45	22	0
Mean	29	18.2	8.4	25	2.1	12.5	5.9	3.2
SD	17	20.2	11.4	26.4	6.6	20.2	12.9	10.1
SEM	5.4	6.4	3.6	8.3	2.1	6.4	4.1	3.2
PROTECTION RATE*	-	**37%**	**71%**	**14%**	**93%**	**57%**	**80%**	**89%**

*Defined by Equation 1

TABLE 2: STATISTICAL ANALYSIS OF DATA BY THE *t-test*

COMPARISON	*p* value
Control vs Fine Pumactant	0.2123
Control vs Coarse Pumactant	0.0052
Control vs propylene glycol	0.6916
Control vs DPPC paste	0.0002
Control vs DPPG paste	0.0639
Control vs DPPC:DPPG, 7:3	0.0031
Control vs DPPC:DPPG, 1:1	0.0006
propylene glycol vs DPPC paste	0.0158
propylene glycol vs DPPG paste	0.2495
propylene glycol vs DPPC:DPPG, 7:3	0.0544
propylene glycol vs DPPC:DPPG, 1:1	0.0251
Fine ALEC vs Coarse Pumactant	0.1978
DPPC paste vs DPPG paste	0.1397
7:3 paste vs 1:1 paste	0.6094
DPPC paste vs 7:3 paste	0.4193
DPPC paste vs 1:1 paste	0.1207
DPPG paste vs 7:3 paste	0.3960
DPPG paste vs 1:1 paste	0.2098
DPPC paste vs Fine Pumactant	0.0277
DPPC paste vs Coarse Pumactant	0.1477
DPPG paste vs Fine Pumactant	0.5361
DPPG paste vs Coarse Pumactant	0.5832
7:3 paste vs Fine Pumactant	0.1222
7:3 paste vs Coarse Pumactant	0.6517

CLAIMS

1. A method of reducing the risk of surgical adhesions which comprises applying a composition comprising a SAPL to membranes adjacent an incision during surgery, characterised in that the SAPL is DPPC, or DPPC and PG or DPPG,, dispersed in a physiologically acceptable non-volatile carrier liquid.

2. Use of a SAPL to prepare a medicament for reducing the risk of adhesions following surgery characterised in that the SAPL is DPPC, or DPPC and PG or DPPG dispersed in a physiologically acceptable non-volatile carrier liquid.

3. Use or method according to claim 1 or 2 in which the SAPL is a mixture of DPPC and PG or DPPG.

4. Use or method according to claim 1 or 2 in which the SAPL is DPPC alone.

5. Use or method according to any preceding claim in which the carrier is propylene glycol.

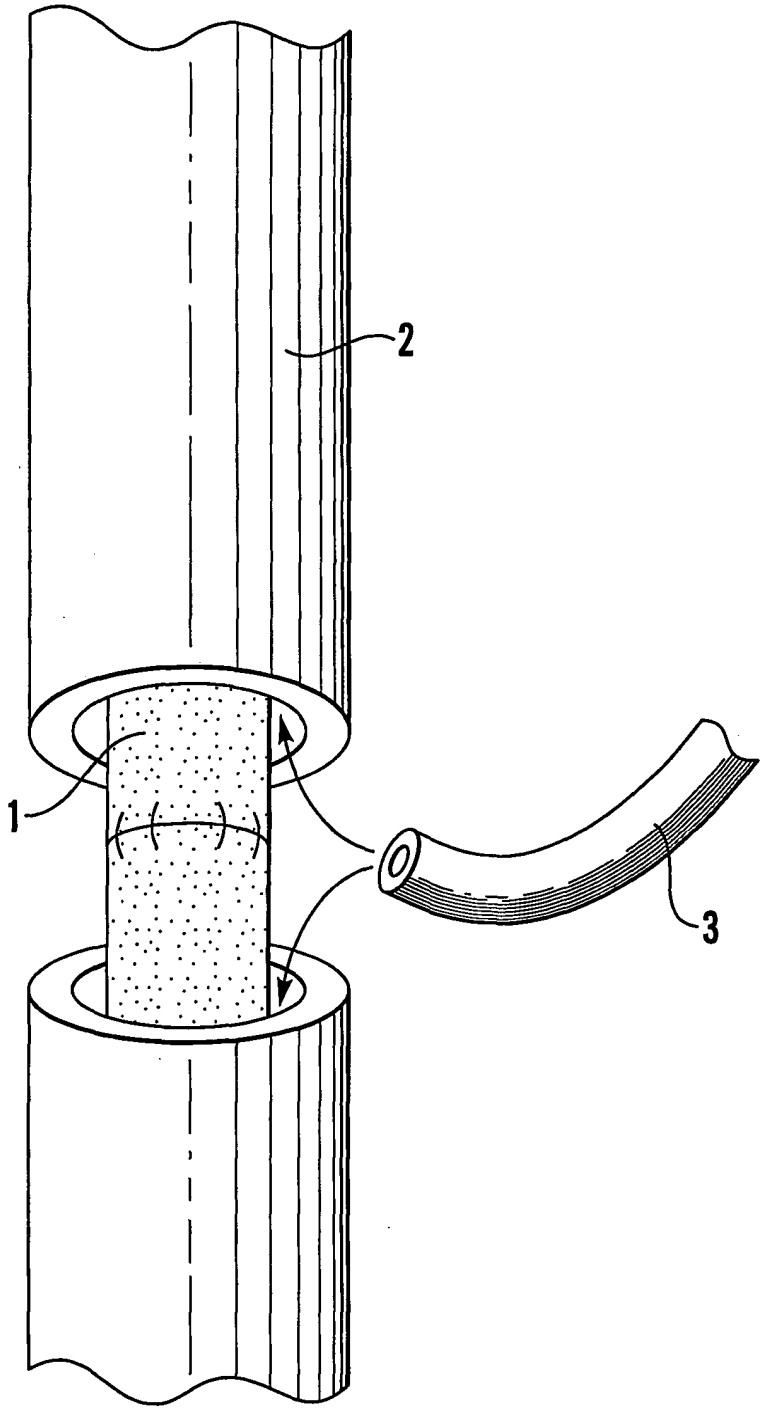
6. Use or method according to any preceding claim in which the SAPL/carrier mixture is in the form of a paste

7. Use or method according to any preceding claim in which the SAPL/carrier mixture is in the form of a paste at ambient temperature but is a liquid at body temperature.

8. Use or method according to any preceding claim in which the paste is formed by cooling a supersaturated solution of SAPL in propylene glycol.

9. Use or method according to any preceding claim in which the SAPL composition is used to prevent adhesions in open surgery.

10. Use or method according to any preceding claim in which the SAPL composition is used to prevent adhesions in spinal surgery, tendon surgery or nerve surgery.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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02915

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P41/00 A61K31/683 A61K31/685 //(A61K31/685,31:683)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 17878 A (LACHMANN BURKHARD ;HAITSMA JOHANNES JACOBUS (NL); WOLLMER PER (SE)) 7 March 2002 (2002-03-07) page 11, line 10 - line 13 page 11, line 26 page 13, line 27 - line 29 page 19, line 20 - line 22 claim 60 ---	1,2,4,6
X	US 6 133 249 A (HILLS BRIAN ANDREW) 17 October 2000 (2000-10-17) cited in the application column 2, line 63 - line 64 column 3, line 57 -column 4, line 2 column 4, line 58 -column 5, line 3 column 5, line 37,41 column 5, line 67 -column 6, line 6 column 13, line 29 - line 31 --- -/--	1,2,4-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2002	18/10/2002

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
.../GB 02/02915

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 12026 A (MACNAUGHT PTY LTD) 22 August 1991 (1991-08-22) cited in the application page 3, paragraphs 4,5 page 4, paragraph 1 page 4-5, table 1 page 5, paragraphs 1,3,4 page 6, paragraphs 4,5 claims 3,5,6	1,2,4-7, 9
X	WO 99 51244 A (HILLS BRIAN ANDREW ;WOODCOCK DEREK ALAN (GB); BRITANNIA PHARMACEUT) 14 October 1999 (1999-10-14) cited in the application page 1, paragraphs 4,7 page 2, paragraph 1 page 3, paragraph 2 page 6, paragraphs 4,6 claims 4-8	1-4
X	WO 98 53800 A (APPLIED BIOTECHNOLOGY INC ;KOROLY MICHAEL V (US)) 3 December 1998 (1998-12-03) page 1, line 11 page 5, line 30 - line 31 page 6, line 4 - line 9 page 9, line 14 page 10, line 29 - line 31 example 1	1,2,4,6, 9,10
X	WO 89 01777 A (MACNAUGHT PTY LTD) 9 March 1989 (1989-03-09) page 3, line 5 - line 9 page 5, line 1,6,7 page 6, line 14 - line 15	1,2,4,9
X	BHANDARKAR D S ET AL: "Spray of phospholipid powder reduces peritoneal adhesions in rabbits." THE AUSTRALIAN AND NEW ZEALAND JOURNAL OF SURGERY. AUSTRALIA MAY 1999, vol. 69, no. 5, May 1999 (1999-05), pages 388-390, XP001095870 ISSN: 0004-8682 cited in the application page 388, chapter "animals" page 389, chapter "experiments" page 389, column 2, last line - page 390, column 1, line 7	1,2,4-9

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INTERNATIONAL SEARCH REPORT

ational Application No
PCT/GB 02/02915

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 58168 A (BROWN COLIN ;ML LAB PLC (GB)) 18 November 1999 (1999-11-18) page 1, line 3 - line 6 page 3, line 28 - line 29 page 6, line 7 - line 8 page 6, line 26 - line 28	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/02915

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 and 3-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02915

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